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09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

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EXAMINER	
ANGELL, JON E	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11,14,15,17-21,24,34,43,56 and 78-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,11,14,15,17-21,24,34,43,56,78-91,94-98 and 100-103* is/are rejected.

7)☒ Claim(s) *92,93,99 and 104* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 4/26/07.

The amendment filed 4/26/07 is acknowledged and has been entered.

Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-104 are currently pending in the application and are addressed herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Reasons for New Rejections

Applicant's amendment filed 4/26/07 is sufficient to obviate the rejection(s) of the previous Office Action (1/26/07). However, upon further consideration, the claims are not deemed to be allowable for the following reasons. First, claim 56 is drawn to a method of treating cancer comprising administering to a subject an unmethylated CpG oligonucleotide in an effective amount to upregulate expression of CD19, CD20 or CD22 tumor antigen in a cancer cell and further administering a human or humanized antibody of IgG1 isotype that binds to the tumor antigen in an effective amount for treating the cancer. As indicated in a previous Office Action (see Office Action 4/20/04), the unmethylated CpG oligonucleotide must be modified (e.g., backbone modified) such that it is resistant to degradation in order for the oligonucleotide to be effective *in vivo*. Second, the specification does not appear to have support for a "human or humanized antibody of IgG1 isotype" that binds to CD19, CD20 or CD22 surface antigen, as is required by claim 56. Third, the claims encompass an unmethylated CpG 6-100 nucleotides in length and having the general formula 5' $X_1X_2CGX_3X_4$ 3' which is effective for upregulating

expression of CD19, CD20 and CD22 in cancer cells (e.g., see claims 1, 24, 34, 43, 56). However, the specification only appears to disclose one specific oligonucleotide of this general formula which upregulates CD19, CD20 and CD22 expression and only in B-cell malignancies: ODN 2006 (SEQ ID NO: 729). Therefore, specification does not disclose a description sufficient to describe the entire genus of oligonucleotides encompassed by the claims which upregulate CD19, CD20 and CD22 expression in cancer cells. Finally, Applicants have asserted that the discovery that the unmethylated CpG oligonucleotide upregulates expression of CD19, CD20 and CD22 is surprising and unexpected. However, claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are not commensurate in scope with the experiments that were found to have unexpected results because the instant claims encompass a genus of oligonucleotides while the examples only disclose that one specific oligonucleotide (SEQ ID NO: 729) upregulates expression of CD19, CD20 and CD22. There is no evidence of record indicating that any oligonucleotide other than SEQ ID NO: 729 would have the ability to upregulate expression of CD19, CD20 and CD22. As such, the evidence of record can only support the notion that SEQ ID NO: 729, but no other CpG oligonucleotide encompassed by the claims, would have the unexpected function (i.e., the ability to upregulate expression of CD19, CD20 and CD22 in B-cell malignancies). Since, at the time of filing, it was unexpected that a CpG oligonucleotide could upregulate expression of CD19, CD 20 and CD22, claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are enabled only for using SEQ ID NO: 729 in an effective amount to upregulate CD19, CD20 and CD22 expression in B-cell malignancies.

New Rejections

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or

not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

Claim 56 is drawn to a method for treating cancer in a human, wherein cells of the cancer have low or no baseline expression of a surface antigen selected from CD 19, CD20, and CD22, the method comprising: administering to the human an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long, said nucleic acid comprising at least the formula 5' XI-X2-C-G-X3-X4 3', wherein C is unmethylated and wherein X1, X2, X3, and X4 are nucleotides, in an effective amount to upregulate expression of the surface antigen by the cancer; and administering to the human a human or humanized antibody of IgG1 isotype, which antibody binds to the surface antigen, in an effective amount for treating the cancer.

Accordingly, the claim encompasses administering a human or humanized antibody of IgG1 isotype which binds to CD19, CD20, CD22 antigen. However, the specification has been thoroughly searched but neither explicit nor implicit support for human or humanized antibodies of IgG1 isotype which bind to CD19, CD20 and CD22 antigen could not be found. Should Applicants traverse this rejection, they are asked to identify the specific page and line number(s) where support for the indicated limitation can be found.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claim 56 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

3. Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the claims encompass a method that comprises administering a nucleic acid comprising at least the formula 5' XI-X2-C-G-X3-X4 3', wherein C is unmethylated and wherein X1, X2, X3, and X4 are nucleotides, in an effective amount to upregulate expression of CD19, CD20 or CD22 surface antigen in cancer cells (it is noted that claim 56 encompasses any type of cancer cell while the other claims are limited to B-cell malignancies). Therefore, the claims encompass a genus of oligonucleotides which upregulate expression of CD19, CD20 and CD22 in cancer cells. It is noted that Applicants contend that the fact that an unmethylated CpG oligonucleotide upregulates CD19, CD20 and CD22 expression in B-cell malignancies is surprising and unexpected. For instance, page 11 (paragraph 0046 of the specification) states:

> "The invention is based, in part, on the surprising discovery that administration to a subject of immunostimulatory nucleic acids induces the expression of cell surface antigens including CD20, CD19, and CD22 on the surface of a cancer cell and that the induction of these antigens leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). It was previously believed that CpG oligonucleotides enhanced ADCC by influencing the effector cell (e.g., by activating natural killer (NK) cells). Now it has been

> discovered according to the invention that immunostimulatory nucleic acids actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies."

Furthermore the Examples disclosed in the specification only disclose one specific oligonucleotide which has the ability to upregulate surface antigens in tumor cells, ODN 2006 (SEQ ID NO: 729). Furthermore, the Examples and evidence of record indicate only that SEQ ID NO: 729 upregulated expression of CD19, CD20 and CD22 in B-cell malignancies and not other cancer (e.g., see Example 1, Figure 1, Figure 3). There is no indication that any other oligonucleotide was able to upregulate expression of a surface antigen in a cancer cell. Considering that it was surprising and unexpected that SEQ ID NO: 729 was able to upregulate expression of CD19, CD20 and CD22 in most B-cell malignancies, the disclosure is sufficient to describe only one oligonucleotide that meets the structural limitations of the claims and which upregulates expression of CD19, CD20, CD22 in C-cell malignancies: ODN 2006 (SEQ ID NO: 729). Considering that ODN 2006 is the only oligonucleotide which has been disclosed as having the required function, it is impossible to determine if any other oligonucleotide that meets the structural limitations of the claims would have the required activity without performing additional experimentation. Furthermore, since the control oligonucleotide was a poly-C oligonucleotide, it is impossible to tell if it is unmethylated CpG motif of ODN 2006 or some other aspect of the oligonucleotide which confers its surprising function.

Therefore, the specification does not contain a sufficient recitation of distinguishing identifying characteristics to provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the oligonucleotide sequence that is SEQ ID NO: 729 meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the growth of a B-cell malignancy, said method comprising administering to a subject having the B-cell malignancy:

a) administering an immunostimulatory nucleic acid sequence to the subject in an amount effective to upregulate expression of CD20, CD19 or CD22 surface antigen in cancer cells of the

B-cell malignancy wherein the immunostimulatory nucleic acid sequence is SEQ ID NO: 729 and wherein the immunostimulatory nucleic acid sequence comprises an unmethylated CpG motif and wherein the nucleic acid sequence further comprises a backbone modification; and

b) an antibody specific for the surface antigen which is upregulated in response to administration of the immunostimulatory oligonucleotide;

wherein administration of the immunostimulatory nucleic acid and the antibody results in the inhibition of the growth of the B-cell malignancy;

does not reasonably provide enablement for entire scope of the instant claims. For instance, the specification does NOT provide enablement for: (1) using an immunostimulatory nucleic acid sequence that does not comprise a modified backbone (as is encompassed by claim 56), (2) upregulating expression of CD19, CD20 or CD22 in any cells other than cells of a B-cell malignancy (as is encompassed by claim 56), (3) 1) **preventing** cancer in subject a subject (as is encompassed by claim 56), and (4) using any oligonucleotide encompassed by the claims other than SEQ ID NO: 729 (as is encompassed by all of the instant claim). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of the claims:

In their broadest embodiments (e.g., claim 56) the instant claims encompass a method of treating cancer comprising: administering to a subject (a) an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long and comprising at least the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated and wherein X_1 X_2 X_3 and X_4 are nucleotides, in an amount effective to upregulate CD20, CD19 or CD 22 expression and b) and an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody in an effective amount to treat the cancer. Therefore, the general nature of the invention is cancer immunotherapy and encompasses administering a combination of an antibody and an immunostimulatory nucleic acid. Since claim 56 does not explicitly indicate that the subject has cancer, the claim encompasses "treating" a subject at risk of developing any type of cancer (i.e., preventing any type of cancer).

The unpredictability of the art and the state of the prior art:

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs, 1998; 5:341-346, previously of record) teaches,

> "Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity." (See p. 342, first paragraph).

Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121, previously cited) teaches that sequences required for CpG related immune stimulation varies from species to species, and specifically indicates, "The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT" (See p. 115, first paragraph). Thus indicating there is variability in the efficacy in the immunostimulatory oligonucleotides encompassed by the claims.

Importantly, Hartmann et al. (J. Immunology, 2000; 164:1617-1624, previously cited) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches,

> "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (See p. 1618, first column).

Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

There is no teaching in the prior or post-filing art indicating that any cancer can be prevented without any chance of occurrence, thus indicating the high degree of unpredictability of preventing cancer. In fact, methods for curing/preventing cancer would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

Working Examples and Guidance in the Specification

The specification has one working example specifically indicating that one specific unmethylated CpG oligonucleotide, ODN 2006 (SEQ ID NO: 729) had the ability to upregulate expression of CD19, CD20 and CD22 in malignant human B-cells (e.g., see Example 1). It is acknowledged that Example 3 indicates that the combination of ODN 1826 and a mouse IgG2a monoclonal antibody (MS11G6) significantly improved survival of mice having tumors compared to control mice (see, pages 76-77). However, in view of the teaching of Agrawal et al. (indicated above) the result does not necessarily indicate that the ODN 1826 would have the same effect on human tumor cells. There is no evidence that ODN 1826 increased expression of CD19, CD20 or CD22 in the mice tumor cells. Furthermore, there is no evidence that any oligonucleotide other than the unmethylated ODN 2006 upregulated expression of CD19, CD20 or CD22 in tumor cells.

Also, there are no examples or guidance disclosing the method as useful for treating any kind of cancer other than B-cell malignancies and there is no example/guidance indicating that B-cell malignancy can be prevented.

The data presented in the specification indicate that the discovery that an unmethylated CpG oligonucleotide can upregulate expression of CD19, CD20 and CD22 in tumor cells is "surprising". It is accepted that this finding is surprising, and thus unexpected. However, considering that the result is unexpected, the specification only provides enablement for the disclosed protocol which confers the unexpected result. That is, since the results are unexpected, the only embodiments of the claims which the specification enables is a method for treating a subject having a B-cell malignancy comprising administering an immunostimulatory oligonucleotide that is ODN 2006 (SEQ ID NO: 729) wherein the oligonucleotide comprises an

unmethylated CpG motif wherein the oligonucleotide is administered in an effective amount to upregulate expression CD19, CD20 or CD22 surface antigen in cells of said B-cell malignancy and further comprising administering an antibody that is specific for the surface antigen whose expression is upregulated.

Quantity of Experimentation

Considering the breadth of the claims and the limited working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims. For instance, considering the prior art teachings and the examples/guidance provided in the specification, additional experimentation would be required in order to use any immunostimulatory oligonucleotide other than an ODN 2006 comprising an unmethylated CpG motif and further comprising a backbone modification to upregulate expression of CD19, CD20 or CD22 in B-cell malignancies, let alone another other type of cancer. For instance, one would have to show how a nucleic acid comprising an unmethylated CpG motif, but without backbone modification could function as an immunostimulatory molecule. Considering the teaching in the art that it is imperative for the oligonucleotide to have a modified backbone in order to protect the oligonucleotide from degradation by nucleases.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability of recognized in the art indicated above; 2) the breadth of the claims; 3) the limited working examples and guidance in the

specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed to the full scope encompassed by the claims is undue.

Claim Objections

5. Claims 92, 93, 99 and 104 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
Art Unit 1635